General

Guideline Title

Inherited thrombophilias in pregnancy.

Bibliographic Source(s)

American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2013 Sep. 12 p. (ACOG practice bulletin; no. 138). [69 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2011 Sep. 11 p. (ACOG practice bulletin; no. 124). [66 references]

Recommendations

Major Recommendations

The grades of evidence (I-III) and levels of recommendations (A-C) are defined at the end of "Major Recommendations" field.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Warfarin, low-molecular-weight heparin (LMWH), and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant; therefore, these anticoagulants may be used in women who breastfeed.
- Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear if anticoagulation reduces recurrence.
- There is insufficient evidence to either screen for or treat women with inherited thrombophilias and obstetric histories that include complications such as fetal growth restriction or preeclampsia.
- Because of the lack of association between either heterozygosity or homozygosity for the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and any negative pregnancy outcomes, including any increased risk for venous thromboembolism, screening with either *MTHFR* mutation analyses or fasting homocysteine levels is not recommended.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin *G20210A* mutation; and antithrombin, protein C, and protein S deficiencies.
- Treatment recommendations for women with inherited thrombophilias are listed in the table below.

- All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions.

Table: Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophilia with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation	Prophylactic or intermediate-dose LMWH/UFH or surveillance without anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Surveillance without anticoagulation therapy or prophylactic LMWH or UFH	Postpartum anticoagulation therapy
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen	Postpartum anticoagulation therapy or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)
No thrombophilia with previous single episode of VTE associated with transient risk factor that is no longer present—Excludes pregnancy- or estrogen-related risk factor	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy‖
No thrombophilia with previous single episode of VTE associated with transient risk factor that was pregnancy or estrogen related	Prophylactic-dose LMWH or UFH‖	Postpartum anticoagulation therapy
No thrombophilia with previous single episode of VTE without an associated risk factor (idiopathic)—Not receiving long-term anticoagulation therapy	Prophylactic LMWH or UFH‖	Postpartum anticoagulation therapy
Thrombophilia or no thrombophilia with two or more episodes of VTE–Not receiving long-term anticoagulation therapy	Prophylactic or therapeutic-dose LMWH or Prophylactic or therapeutic-dose UFH	Postpartum anticoagulation therapy or Therapeutic-dose LMWH/UFH for 6 weeks
Thrombophilia or no thrombophilia with two or more episodes of VTE–Receiving long-term anticoagulation therapy	Therapeutic-dose LMWH/UFH	Resumption of long-term anticoagulation therapy

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism

*Postpartum treatment levels should be greater or equal to antepartum treatment. Treatment of acute VTE and management of antiphospholipid syndrome are addressed in other Practice Bulletins.

†Low-risk thrombophilia: factor V Leiden heterozygous; prothrombin *G20210A* heterozygous; protein C or protein S deficiency.

‡First-degree relative with a history of a thrombotic episode before age 50 years, or other major thrombotic risk factors (e.g., obesity, prolonged immobility).

§High-risk thrombophilia: antithrombin deficiency; double heterozygous for prothrombin *G20210A* mutation and factor V Leiden; factor V Leiden homozygous or prothrombin *G20210A* mutation homozygous.

‖Surveillance without anticoagulation is supported as an alternative approach by some experts.

Definitions:

Grades of Evidence

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Levels of Recommendations

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Inherited thrombophilias:
  - Factor V Leiden mutation
  - Prothrombin *G20210A* mutation
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
  - Methylenetetrahydrofolate reductase mutations
- Pregnancy
- Venous thromboembolism

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Hematology

Medical Genetics

Obstetrics and Gynecology

Pharmacology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To review common thrombophilias and their association with maternal venous thromboembolism risk and adverse pregnancy outcomes, indications for screening to detect these conditions, and management options in pregnancy

Target Population

Pregnant, postpartum, and breastfeeding women with inherited thrombophilias

Interventions and Practices Considered

Risk Assessment/Screening

1. Patient and family history
2. Individualized risk assessment
3. Screening for inherited thrombophilias:
    - Factor V Leiden mutation
    - Prothrombin *G20210A* mutation
    - Protein C deficiency
    - Protein S deficiency
    - Antithrombin deficiency

Note: Screening with methylenetetrahydrofolate reductase (MTHFR) polymorphisms or measurement of fasting homocysteine levels was considered but not recommended.

Management/Treatment

1. Low-molecular-weight heparin (LMWH)
2. Unfractionated heparin
3. Warfarin
4. Surveillance
5. Compression stockings/pneumatic compression boots
6. International normalized ratio (INR) monitoring

Major Outcomes Considered

- Incidence of venous thromboembolism
- Adverse pregnancy outcomes
- Adverse effects of therapy

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and January 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Analysis of available evidence was given priority in formulating recommendations. When reliable research was not available, expert opinions from obstetrician-gynecologists were used. See also the "Rating Scheme for the Strength of the Recommendations" field regarding Level C recommendations.

Rating Scheme for the Strength of the Recommendations

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A — Recommendations are based on good and consistent scientific evidence.

Level B — Recommendations are based on limited or inconsistent scientific evidence.

Level C — Recommendations are based primarily on consensus and expert opinion.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Practice Bulletins are validated by two internal clinical review panels composed of practicing obstetrician-gynecologists generalists and subspecialists. The final guidelines are also reviewed and approved by the American College of Obstetricians and Gynecologists (ACOG) Executive Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate management of inherited thrombophilias in pregnancy
- Decreased maternal venous thromboembolism risk
- Reduction of adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption

Potential Harms

- Bleeding risks associated with anticoagulation therapy
- To avoid paradoxical thrombosis and skin necrosis from the early antiprotein C effect of warfarin, women should continue to take therapeutic doses of unfractionated heparin or low-molecular-weight heparin (LMWH) for 5 days and until the international normalized ratio (INR) is therapeutic (2.0–3.0) for 2 consecutive days.

Qualifying Statements

Qualifying Statements

The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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of Obstetricians and Gynecologists (ACOG); 2013 Sep. 12 p. (ACOG practice bulletin; no. 138). [69 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Apr (revised 2013 Sep)

Guideline Developer(s)

American College of Obstetricians and Gynecologists - Medical Specialty Society

Source(s) of Funding

American College of Obstetricians and Gynecologists (ACOG)

Guideline Committee

American College of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins—Obstetrics

Composition of Group That Authored the Guideline

This Practice Bulletin was developed by the Committee on Practice Bulletins—Obstetrics with the assistance of Charles Lockwood, MD, George Wendel, MD, and Neil Silverman, MD.

American College of Obstetricians and Gynecologists (ACOG) committees are created or abolished and their overall function defined by the Executive Board. Appointments are made for one year, with the understanding that such appointment may be continued for a total of three years. The majority of committee members are Fellows, but Junior Fellows also are eligible for appointment. Some committees may have representatives from other organizations when this is particularly appropriate to committee activities. The president elect appoints committee members annually.

Financial Disclosures/Conflicts of Interest

Not stated

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Guideline Availability

Electronic copies: None available

Print copies: Available for purchase from the American College of Obstetricians and Gynecologists (ACOG) Distribution Center, PO Box 933104, Atlanta, GA 31193-3104; telephone, 800-762-2264; e-mail: sales@acog.org. The ACOG Bookstore is available online at the ACOG Web site.

Availability of Companion Documents

A proposed performance measure is included in the original guideline document.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 16, 2010. This NGC summary was updated by ECRI Institute on October 21, 2011. This NGC summary was updated by ECRI Institute on October 25, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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